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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,574	07/20/2001	Frank A. Skraly	MBX 039	2982

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EXAMINER

PAK, YONG D

ART UNIT	PAPER NUMBER
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1652

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

09/909,574

Applicant(s)

SKRALY ET AL.

Examiner

Yong D. Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/26/2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 6-10 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 6-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment filed on December 26, 2006, has been entered.

Claims 1-4 and 6-10 are pending and are under consideration.

Response to Arguments

Applicant's arguments filed December 26, 2006 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4 and 6-10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Skraly, Madison et al., and BRENDA database.

Claims 1-4 and 6-10 are drawn to a method of producing PHAs by providing an *E. coli*, which expresses acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase or PHA synthase, wherein said bacteria is genetically engineered to express polynucleotides that encode a diol oxidoreductase or aldehyde dehydrogenase, wherein the enzyme expressed by the bacteria convert 1,6-hexandiol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol or 1,2-propanediol into 6-

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hydroxyhexanoate, 5-hydroxyvalerate, 4-hydroxybutyrate, 2-hydroxyethanoate or 2-hydroxypropionate monomers, respectively, and producing PHAs having a weight-average molecular weight of at least 300,000 Da.

Skrally (*Polyhydroxyalkanoates Produced by Recombinant E. coli*, Poster at Engineering Foundation Conference: Metabolic Engineering, 1998 – cited previously on form PTO-892) discloses a method of producing PHA from 1,3-propanediol using recombinant *E. coli* expressing PHA synthase and diol oxidoreductase (pages 8-9), wherein said diol is oxidized to its corresponding aldehyde and then converted to its corresponding hydroxyalkanoate monomer via an aldehyde dehydrogenase and CoA transferase (page 8). *E. coli* produces aldehyde dehydrogenase naturally (see “aldehyde dehydrogenase” – cited previously on form PTO-892). Skrally also discloses (1) PHA monomers other than 3-hydroxybutyrate that can improve flexibility and reduce crystallinity of the resulting PHA polymer, such as 5-hydroxyvalerate and 4-hydroxybutyrate (page 6) and (2) new inexpensive starting materials for PHA synthesis, such as diols, 1,3-propanediol, 1,5-pentanediol, 1,4-butanediol and 1,2-propanediol, which are converted into their respective PHA monomers, 3-hydroxybutyrate, 5-hydroxyvalerate, 4-hydroxybutyrate and 2-hydroxypropionate (pages 1, 6 and page 8).

The difference between the reference of Skrally and the instant invention is that the reference of Skrally ~~teaches~~ does not teach a method of producing PHA from 1,6-hexanediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol and 1,2-propanediol using an *E. coli* expressing diol oxidoreductase and acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase or PHA synthase.

Madison et al. (Metabolic engineering of poly(3-hydroxyalkanoates): from DNA to plastic. *Microbiol Mol Biol Rev.* 1999 Mar;63(1):21-53 – form PTO-1449) is cited here to provide evidence to support the level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs. Madison et al. also teaches that the molecular mass of PHAs produced varies from 50,000 to 1,000,000 Da and bacterially produced PHAs have a high molecular mass (page 22). As applicants have stated, “one of skill in the art was capable of making and using genetically engineered plants for production of PHAs... all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells” (Appeal Brief, pages 24-25).

BRENDA database (“EC 1.1.1.202” – form PTO-892) discloses several diol reductases that oxidize diols and that have been cloned and expressed in *E. coli*, including the *K. pneumoniae* diol oxidoreductase used by Skraly and in the instant invention. Further, BRENDA database discloses a 1,3-propanediol dehydrogenase isolated from *C. freundii* which oxidizes several diols, 1,3-propanediol, 1,2-propanediol and 1,4-butanediol, and its expression in *E. coli* (pages 2-3). This enzyme has been cloned and expressed in *E. coli* (pages 10 and 12) as evidenced by Daniel et al. (*J Bacteriol.* 1995 Apr;177(8):2151-6 - form PTO-892). Daniel et al. also teaches that said enzyme oxidizes all primary, secondary and tertiary alcohols (Daniel et al. on page 5152). Even though 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol are not

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explicitly listed as one of the substrates, since the enzyme is able to oxidize primary alcohols and diols containing two primary alcohols, one having ordinary skill in the art would have reasonably expect the enzymes to oxidize 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol. Also, one having ordinary skill in the art would have used other diol reductases of BRENDA database to oxidize the recited diols.

Therefore, combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art to use the method of Skraly et al. in making PHAs by using other diols, such as 1,6-hexandediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol or 1,2-propanediol, by converting said diols into their respective PHA monomers using a recombinant *E. coli* that expresses acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase or PHA synthase as taught by Madison et al, and that also expresses a diol oxidoreductase. One of ordinary skill in the art would have been motivated to produce PHA from the recited diols in order to produce novel PHAs using inexpensive starting materials. One of ordinary skill in the art would have had a reasonable expectation of success since Skraly teaches a method of producing PHAs from a diol using a diol oxidoreductase/aldehyde dehydrogenase, Madison et al. teaches expression of genes necessary for PHA synthesis and BRENDA database teaches several diol oxidoreductases that have been cloned into *E. coli* that have a wide range in substrate specificity. One having ordinary skill in the art would have had a reasonable expectation of success since production of PHAs in recombinant organism, such as *E. coli*, expressing enzymes necessary for PHA production is well known in the art and diol

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oxidoreductases, which have been cloned and expressed in *E. coli*, having a wide range of substrate specificity are well known in the art.

Therefore, the above references render claims 1-4 and 6-10 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims are not obvious over the cited references because Skraly does not disclose a method that can convert diols into 6-hydroxyhexanoate (1,6-hexanediol), 5-hydroxyvalerate (1,5-pentanediol), 4-hydroxybutyrate (1,4-butanediol), 2-hydroxyethanoate (1,2-ethanediol) and 2-hydroxypropionate (1,2-propanediol). Examiner respectfully disagrees. Skraly discloses new routes for producing PHAs, such as 1,2-propanediol (converted to 2-hydroxypropionate), 1,4-butanediol (converted to 4-hydroxybutyrate) and 1,5-pentanediol (converted to 5-hydroxyvalerate) (pages 1, 6-7 and 9). Since Skraly discloses new monomers/starting materials and routes for PHA synthesis of Skraly, it would have been obvious to one having ordinary skill in the art to generate PHAs comprising of 5-hydroxyvalerate, 4-hydroxybutyrate or 2-hydroxypropionate from 1,5-pentanediol, 1,4-butanediol or 1,2-propanediol, respectively, or convert other structurally similar diols, such as 1,6-hexanediol into 6-hydroxyhexanoate and 1,2-ethanediol into 2-hydroxyethanoate by using *E. coli* expressing diol oxidoreductase available in the art.

Applicants also argue that Madison et al. and Brenda database do not teach converting diols into PHA monomers. The rejection is based on the combined

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teachings of Skraly, Madison and BRENDA. The reference of Madison is used for its disclosure of supporting the level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs and the reference of Brenda database is used for its teaching of many diol oxidoreductases available to one having ordinary skill in the art. Skraly et al. provides teachings of converting diols into PHA monomers.

Applicants also argue use of improper hindsight reasoning. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, it should be noted that as applicants have stated, "one of skill in the art was capable of making and using genetically engineered plants for production of PHAs... all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells" (Appeal Brief, pages 24-25). Madison et al. provides evidence to support the level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs. Also, since knowledge of making PHA from a diol, 1,3-propanediol, using a

recombinant *E. coli* expressing a diol oxidoreductase and genes necessary in PHA synthesis was well known, a method of making PHA from other diols was well within the level of one having ordinary skill in the art at the time the invention was made.

Hence the rejection is maintained.

Conclusion

None of the claims are allowable

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax

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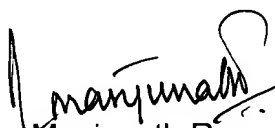
phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).



Yong D. Pak
Patent Examiner 1652



Manjunath Rao
Primary Patent Examiner 1652